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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/006,290	10/22/2001	Jay Wohlgemuth	506612000100	8497

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EXAMINER	
SISSON, BRADLEY L	
ART UNIT	PAPER NUMBER
1634	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/006,290	WOHLGEMUTH ET AL.	
	Examiner	Art Unit	
	Bradley L. Sisson	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *55-66 and 68-72* is/are pending in the application.

4a) Of the above claim(s) *56-65* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *55,66 and 68-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Claims 56-65 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 22 November 2005.

2. It is further noted that in said response, applicant elected the nucleic acid corresponding to SEQ IDNO: 4758. Accordingly, SEQ ID NOs. 3702, 2073, 213, 3028, 6299, 832, 2143, 3651, and 3750, which appear in amended claim 1, remain withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention.

3. This application contains claims 56-65, drawn to an invention nonelected with traverse in response received 22 November 2005. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

5. Acknowledgement is made of applicant having amended the title in their response of 19 October 2006; however, none of the pending claims are limited to the use of "Leukocyte Expression Profiling."

6. The abstract of the disclosure is objected to because none of the pending claims are limited to the use of leukocytes in any manner, much less leukocyte gene expression profiling. Correction is required. See MPEP § 608.01(b).

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 55, 66, and 68-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. As set forth in *Enzo Biochem Inc., v. Calgene, Inc.* (CAFC, 1999) 52 USPQ2d at 1135, bridging to 1136:

> To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' " *Genentech, Inc. v. Novo Nordisk, A/S*, 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997) (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Whether claims are sufficiently enabled by a disclosure in a specification is determined as of the date that the patent application was first filed, see *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986).... We have held that a patent specification complies with the statute even if a "reasonable" amount of routine experimentation is required in order to practice a claimed invention, but that such experimentation must not be "undue." See, *e.g.*, *Wands*, 858 F.2d at 736-37, 8 USPQ2d at 1404 ("Enablement is not precluded by the necessity for some experimentation . . . However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' ") (footnotes, citations, and internal quotation marks omitted). In *In re*

> *Wands*, we set forth a number of factors which a court may consider in determining whether a disclosure would require undue experimentation. These factors were set forth as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. *Id.* at 737, 8 USPQ2d at 1404. We have also noted that all of the factors need not be reviewed when determining whether a disclosure is enabling. See *Amgen, Inc. v. Chugai Pharm. Co., Ltd.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991) (noting that the *Wands* factors "are illustrative, not mandatory. What is relevant depends on the facts.").

The quantity of experimentation necessary,

The quantity of experimentation is great, on the order of several man-years with little if any reasonable expectation of success.

The amount of direction or guidance presented,

The specification has been found to teach a variety of procedures, generally focused on the use of leukocyte expression assay, the analysis that flows therefrom. The presently claimed invention, however, does not require the use of any leukocyte expression analysis. Indeed, the sample of RNA to be used in the claimed method can fairly cone from any tissue in the affected individual and bar no relationship to the actual source of the RNA. The specification has not been found to set forth an accurate and reproducible procedure whereby one of skill in the art can diagnose or monitor rejection of any tissue in any organism.

The presence or absence of working examples,

The specification has been found to comprise 24 examples. Pages 102-103 provide an index of said examples, which for convenience, is reproduced below.

Example 1: Generation of subtracted leukocyte candidate nucleotide library

Example 2: Identification of nucleotide sequences for candidate library using data mining techniques

Example 3: DNA Sequencing and Processing of raw sequence data.

Example 4: Further sequence analysis of novel nucleotide sequences identified by subtractive hybridization screening

Example 5: Further sequence analysis of novel Clone 596H6

Example 6: Further sequence analysis of novel Clone 486E11

Example 7: Preparation of a leukocyte cDNA array comprising a candidate gene library

Example 8: Preparation of RNA from mononuclear cells for expression profiling

Example 9: Preparation of Buffy Coat Control RNA for use in leukocyte expression profiling

Example 10. RNA Labeling and hybridization to a leukocyte cDNA array of candidate nucleotide sequences.

Example 11: Identification of diagnostic gene sets useful in diagnosis and treatment of Cardiac allograft rejection

Example 12: Identification of diagnostic nucleotide sets for kidney and liver allograft rejection

Example 13: Identification of diagnostic nucleotide sequences sets for use in the diagnosis and treatment of Atherosclerosis, Stable Angina Pectoris, and acute coronary syndrome.

Example 14: Identification of diagnostic nucleotide sets for use in diagnosing and treating Restenosis

Example 15: Identification of diagnostic nucleotide sets for use in monitoring treatment and/or progression of Congestive Heart Failure

Example 16: Identification of diagnostic nucleotide sets for use in diagnosis of rheumatoid arthritis.

Example 17: Identification of diagnostic nucleotide sets for diagnosis of cytomegalovirus

Example 18: Identification of diagnostic nucleotide sets for diagnosis of Epstein Barr Virus

Example 19: Identification of diagnostic nucleotides sets for monitoring response to statin drugs.

Example 20: Probe selection for a 24,000feature Array.

Example 21: Design of oligonucleotide probes.

Example 22: Production of an array of 8, 000 spotted 50 mer oligonucleotides.

Example 23: Amplification, labeling and hybridization of total RNA to an oligonucleotide microarray.

Example 24:Analysis of Human Transplant Patient Mononuclear cell RNA Hybridized to a 24, 000 Feature Microarray.

As can be seen above, none of the examples relate directly to the presently claimed method. Further review of the specification fails to locate where applicant has set forth starting materials and reaction conditions whereby one would be able to enable the full scope of the now claimed invention. While applicant asserts at page 10 of the response of 19 October 2006 that the specification teaches at page 29 and at page 33 how one could determine the level of RNA transcribed, the method is not limited to performing just this step. Rather, the claimed method requires one to be able to diagnose any transplant rejection in any organism.

The specification also fails to take into account any medication the patient may be on, their age, gender, other illnesses, or medications. Page 183 of the specification provides a listing of contemplated transplants, which for convenience, is reproduced below.

Transplant Rejection	Heart
	Lung
	Liver
	Pancreas
	Bowel
	Bone Marrow
	Stem Cell
	Graft versus host disease
	Transplant vasculopathy
	Skin
	Cornea
	Immunosupressive drug use

The specification is silent as to how any accurate and reproducible diagnosis can be made for any of these listed transplants, much less other tissues, or for any tissue in any non-human transplant recipient.

The situation at hand is analogous to that in *Genentech v. Novo Nordisk A/S* 42 USPQ2d 1001. As set forth in the decision of the Court:

> " '[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.' *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *see also Amgen Inc. v. Chugai Pharms. Co.*, 927 F. 2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed Cir. 1991); *In re Fisher*, 427 F. 2d 833, 166 USPQ 18, 24 (CCPA 1970) ('[T]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.').
>
> *****
>
> "Patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. *See*

> *Brenner v. Manson*, 383 U.S. 519, 536, 148 USPQ 689, 696 (1966) (stating, in context of the utility requirement, that 'a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.') Tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention.
>
> "It is true . . . that a specification need not disclose what is well known in the art. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research. (Emphasis added)

The nature of the invention,

The claimed invention relates directly to matters of physiology and chemistry, which are inherently unpredictable and as such, require greater levels of enablement. As noted in *In re Fisher* 166 USPQ 18 (CCPA, 1970):

> In cases involving predictable factors, such as that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.

More particularly, the claimed method relates to the accurate and reproducible determination of whether a transplant of any given tissue will be rejected by a host. The sample may come from

virtually any tissue, and have no direct or indirect bearing on the transplant, yet, as encompassed by the claim, the diagnosis of the individual can still be effective.

The breadth of the claims.

The claims encompass the accurate and reproducible diagnosis of transplant rejection or acceptance in any living organism, be it human or not, and where any one or more tissues may have been transplanted, and where the sample isolated for analysis may have no bearing on the transplant. The method also fairly encompasses said diagnosis and monitoring where no detectable level is used, and no correlation is drawn from any results obtained and the state or prognosis of the patient. Indeed, as presently worded, claims 69 through 71 recite various means by which "said RNA level is determined," however, none of the methods require any label, and at no time doe the claims recite any method step requiring any correlation to be drawn between the determined RNA level and the condition of the transplant and the likelihood that it will be accepted or rejected by a host.

10. In view of the breadth of scope clamed, the limited guidance provided, the unpredictable nature of the art to which the claimed invention is directed, and in the absence of convincing evidence to the contrary, the claims are deemed to be non-enabled by the disclosure.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

12. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bradley L. Sisson whose telephone number is (571) 272-0751. The examiner can normally be reached on 6:30 a.m. to 5 p.m., Monday through Thursday.

14. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

B. L. Sisson

Bradley L. Sisson
Primary Examiner
Art Unit 1634

BLS